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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/922,240	08/27/1997	STUART L. SCHREIBER	APBI-P01-007	1342

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EXAMINER
SORBELLO, ELEANOR

ART UNIT	PAPER NUMBER
1632	24

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/922,240	Applicant(s) SCHREIBER ET AL.	
	Examiner Eleanor Sorbello	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sh t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,29-33,36 and 38-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *32,33,36 and 44* is/are allowed.

6)☒ Claim(s) *1-27,29-31 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to amendment

1. Applicant's amendment filed 1/15/02, paper number 23 has been entered. Claims 1, 2, 6, 7, 8, 16, 20, 21, 22 have been amended. **Claims 1-27, 29-33, 36, 38-44 are pending. Claims 32, 33, 36 and 44 are allowable as stated in office action dated 4/24/01.** Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendments of the claims and/or applicants argument.

2. Applicant's arguments are addressed below on a per section basis. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1-27, 29-33, 36, 38-39 remain rejected under 35 USC § 112, first paragraph for reasons of record as stated in office action dated 4/15/01 (paragraph 4), as containing subject matter which was not described in the specification in such a manner to enable a skilled artisan to make and use the claimed invention.

Applicants have amended the claims to recite that inhibition of the T cells will occur in a manner dependent on the expression of the mutated MBP. However, applicants claims encompass any mutated MBP. Applicant's amendments have been fully considered but they do not necessarily change the breadth of the claims and context of use.

The claims are directed to a method of inhibiting activation of T cells wherein T cells were engineered ex vivo to express a gene encoding any mutated MBP by contacting the cell with the corresponding macrolide. The claims are further directed to a method of inhibiting transcription of NFAT dependent genes in T cells by engineering the T cells ex vivo to express a gene encoding any mutated MBP by contacting the cell with the corresponding macrolide. The claims further encompass methods of transplantation of the aforesaid engineered cells as a method for reducing graft-versus-host disease (GVHD) which encompasses in-vivo considerations.

As stated in the previous office actions, in view of the breadth of the claims being drawn to the (a) inhibition of the activation of T cells by contacting the cells with any mutated MBP, in the presence of the corresponding macrolide; and (b) in view of the claims drawn to *ex-vivo* gene therapy wherein GVHD is reduced by the adminsitration of the aforementioned transfected cells in the presence of the corresponding macrolide, which encompasses in-vivo considerations; the specification is not enabled.

The claims however, are enabled for *in vitro* transfection of T cells engineered to express a mutated MBP such as mutated cyclosporin, rapamycin and FK506 in the presence of the corresponding macrolide wherein NF-AT dependent genes in the T cells are inhibited.

Because the claims remain directed to a method using a macrolide and any mutated MBP, which ultimately decreases T cell activation via transcription of NFAT dependent genes the claims remain rejected. It remains critical that the macrolide and mutated MBP interact, for the claimed invention to be practiced. Therefore it remains

critical that the nucleotide encodes the mutated MBP and expresses it to a sufficient level and more importantly, that it binds selectively with the macrolide thereby having a Kd less than the wild type resulting in tighter binding than that with the wild type. However, as stated in office actions 4/23/01 and 8/11/00, the claims are unduly broad in that they encompass any mutation. It is not clear that any mutation in a MBP will result in the desired effects unless applicants have teachings in the specification as to how one of skill is to identify mutations that would result in the lowering of the Kd. It appears to the examiner that protein folding due to different mutations is not predictable because one mutation may result in decreased binding while another may result in increased binding unless the teachings support such.

Applicants argue that examiners arguments with regards in vivo engineering are mute. However examiner disagrees because even though the engineering was performed ex vivo, the results of what one would expect when the cells are administered are not clear as discussed in previous office actions with regards how one is to deliver the macrolide etc. and other issues pertaining to in-vivo administration unless applicants show support for such. Applicants argue that examiner has pointed out that the level of expression of the mutated MBP may not be effective to accomplish the intended result. That is only one consideration. Applicants also argue that Bonini have shown biological activity of transduced T cells. However, when these transplanted cells are implanted it is subjected to a complex environment rather than the homogeneous environment in cell culture. Although one article describes ex vivo transfection of PBMCs and subsequent transplantation wherein patient who developed

GVHD were administered gancyclovir, this cannot be extrapolated to any cell transplantation wherein the gene is expected to express in vivo, and a method of reducing GVHD in an animal.

The claims therefore stand rejected for reasons of record due to the unpredictability in the art, the guidance provided, the breadth of the claims and undue experimentation required for one of skill in the art to make and use the instant invention as claimed.

5. Claims 40-43 stand rejected under 35 USC § 112, first paragraph for reasons of record as stated in office action dated 4/15/01 (paragraph 5), as containing subject matter which was not described in the specification in such a manner as to reasonably convey to one skilled in the art that applicants were in possession of the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive.

Claims 40-43 recite methods that require a mutated form of cyclophilin protein and an analog of cyclosporin to bind; or a mutated form of FK 506 and an analog of FK 506 to bind. The next step in the process is that each of the aforesaid dimers bind more selectively with calcineurin than that with which the native forms bind. This would then, according to applicants result in the inhibition of a gene responsive to the signal transduction pathway which would result in decrease in T cell activation.

Applicants argue see page 4, (paragraphs 5-7) of Response dated 1/16/02, that the chosen macrolide is more selective (rather than less selective) for the mutated MBP

than for the wild-type protein. Examiner realizes that the binding is more selective than that for the wild type (rather than less selective as stated in previous office action), but maintains that the issue at hand is that applicants have not described the analogs of cyclosporin, FK506 or rapamycin, that should have a higher binding constant or a lower Kd.

Therefore, in the absence of description of any analogs of cyclosporin, rapamycin or FK506, it is not clear that applicants have adequately described that which they are claiming.

6. Claims 40-43 stand rejected under 35 USC § 112, first paragraph for reasons of record as stated in office action dated 4/15/01 (paragraph 5), as containing subject matter which was not described in the specification in such a manner as to reasonably convey to one skilled in the art to make and use the invention.

Applicants claims are directed to methods of decreasing T cell activation by contacting T cells with a mutated form of MBP ie. mutated FK506, mutated form of cyclosporin or mutated form of rapamycin. As stated in the rejection above, applicants have not described the analogs of mutated FK506, or analogs of the mutated form of cyclosporin or analogs of the mutated form of rapamycin that will reduce T cell activation, and neither did applicants support that which is claimed by experimentation, so as to enable the claimed invention. The claims are directed to methods for increasing the selectivity of binding or decreasing Kd when the macrolide and analog of the mutated form of MBP are brought in contact. However, if the analogs were not

described and experimented with, one of skill in the art will require undue experimentation to identify analogs that would achieve the intended goal of reducing T cell activation.

Applicants argue that the mechanism of reducing T cell activation is primarily mediated by blocking NF-AT dependent gene transcription, and that calcineurin plays a key role in regulating NF-AT dependent gene transcription. Applicants argue that the immunosuppressive effect of these drugs is mediated by the binding of the molecular complex of macrolide and mutated MBP to calcineurin to form a ternary complex, thereby inactivating calcineruin. Applicants further argue that the examples provided teach that T cells were incubated with a construct encoding a mutated cyclophilin, with a mutated cyclosporin, which binds selectively and to a higher degree than with wild-type cyclosporin and induces a biological response in the cell, as evidenced by the inhibiton of transcription of a gene responsive to a signal transductrion pathway that is blocked by cyclosporin. Applicants further argue that the native proteins eg. cyclopylins, and FKBKs and their corresponding native ligands can each be mutated in such a way that they bind selectively to each other and that they do not react with the native macrolide-binding protein.

However, examiner argues that in view of the breadth of the claims directed at any and all analogs of cyclosporin, FK506 or rapamycin, which encompasses any an all changes to the aforesaid MBPs that would result in decreased T cell inhibition, one of skill in the art will require undue experimentation to make and use the claimed analogs. As such applicants are not enabled for that which is claimed.

Conclusion

7. Claims 1-27, 29-31, 38-43 remain rejected.

8. Claims 32, 33, 36 and 44 remain allowable as stated in office action dated 4/24/01.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone

number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED to facilitate further examination.

Deborah Reynolds

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